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A comparison of low versus high heart rate in patients with atrial fibrillation and advanced chronic heart failure: Effects on clinical profile, neurohormones and survival

Michiel Rienstra [a], Isabelle C. Van Gelder [a,*], Maarten P. Van den Berg [a], Frans Boomsma [b], Hans L. Hillege [a], Dirk J. Van Veldhuisen [a]

[a] *Department of Cardiology, Thoraxcenter, University Medical Center Groningen, University of Groningen, P.O. Box 30.001, 9700 RB Groningen, The Netherlands*

[b] *Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands*

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Abstract

Background: Atrial fibrillation is common in chronic heart failure. Long-term restoration of sinus rhythm is generally unsuccessful. It may be speculated that higher heart rates are unfavorable, since this may lead to tachycardiomyopathy, but there are no data which have examined this.
Methods and results: Seventy-seven patients with atrial fibrillation and advanced chronic heart failure, age 70±7 years, left-ventricular ejection fraction 0.23±0.08, 61% with ischemic etiology were included. Patients were dichotomized according to the median heart rate (80 bpm) at inclusion (39 patients with "low" heart rate and 38 patients with "high" heart rate). At baseline, both patient groups were remarkably comparable. After a mean follow-up of 3.3±0.9 years, mortality was comparable (62% versus 55%, *p*=non-significant). An independent relation was found between lower heart rate and survival, in addition to absence of hypertension, digoxin use, and higher N-ANP, dopamine, and renin levels.
Conclusion: In the present analysis, patients with atrial fibrillation and advanced chronic heart failure with higher heart rates are comparable to those with lower heart rates. Not higher heart rates at baseline but, on the contrary, lower heart rates seem associated with a worse outcome.

Keywords: Atrial fibrillation; Chronic heart failure; Heart rate; Neurohormones

Both atrial fibrillation and chronic heart failure are common disorders and often occur together [1–5]. The prevalence of atrial fibrillation increases with progression of chronic heart failure. Data on the influence of atrial fibrillation on mortality in patients with CHF are contradictory, [5–8] but a recent meta-analysis suggests that atrial fibrillation is associated with an increased mortality only in patients with mild to moderate chronic heart failure [3].

Randomized studies showed that rate control is an acceptable treatment strategy for persistent atrial fibrillation [9–12]. Whether this also applies to patients with atrial fibrillation in the setting of chronic heart failure is currently investigated [13]. Although rate control is now often a first choice treatment strategy, also in patients with chronic heart failure, the optimal target heart rate during atrial fibrillation is still unknown. Several small studies reported that high heart rates during atrial fibrillation may induce a so-called tachycardiomyopathy and that conversion to sinus rhythm or adequate rate control may reverse this cardiomyopathy [14]. Also, symptoms and exercise capacity may improve after adequate control of the heart rate [11,15]. On the other hand, left ventricular dysfunction during atrial fibrillation may also occur at normal heart rates [16]. Presumed benefits of a lower heart rate are fewer symptoms, better quality of life, a lower incidence or worsening of heart failure, and better survival. However, more drug related adverse effects and pacemaker implants may occur when higher doses of

* Corresponding author. Tel.: +31 50 3612355; fax: +31 50 3614391.
E-mail address: i.c.van.gelder@thorax.umcg.nl (I.C. Van Gelder).

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rate control drugs are used. Furthermore, recent data show that low heart rates during atrial fibrillation are difficult to achieve [17].

In the present study, we compared the clinical characteristics of patients with advanced chronic heart failure and atrial fibrillation according to heart rate [18–21]. In addition, we investigated outcome during long-term follow-up [22].

1. Methods

1.1. Patient selection

PRIME II was an international survival study with ibopamine in moderate to severe ("advanced") chronic heart failure. Patient enrollment started in 1992, and was prematurely discontinued in 1995 because of a significantly higher fatality rate observed in the ibopamine group compared to the placebo group. After early termination of PRIME II and discontinuation of ibopamine, all the patients, included in the neurohormonal substudy, were followed for another 2 years, until a last assessment, which took place between September 1997 and September 1998. The neurohormonal substudy was performed in The Netherlands [19,20]. In PRIME II, patients with symptoms at rest or a recent hospital admission for chronic heart failure, according to the New York Heart Association (NYHA) functional class III to IV and left ventricular impairment, all on optimal treatment of chronic heart failure were included. Left ventricular impairment was proved by 1 of the following: (1) left ventricular ejection fraction <0.35; (2) left ventricular end-diastolic diameter >60 mm; (3) left ventricular fractional shortening <20%; or (4) cardiothoracic ratio on standard chest x-ray >0.50. Patients were on optimal medical treatment for chronic heart failure, including angiotensin-converting-enzyme inhibitors and diuretics, and, if indicated, digitalis and beta-blockers.

In the present analysis we studied only patients with atrial fibrillation who were included in the neurohormonal substudy of PRIME II. Atrial fibrillation patients were identified by 2 consecutive electrocardiograms, at least 7 days apart. Heart rate in these atrial fibrillation patients was measured by a 12-lead electrocardiogram performed at study baseline. Methods of neurohormonal measurements have been published in detail previously [19,21]. Institution of negative chronotropic drugs for control of the ventricular rate during atrial fibrillation was led to the discretion of the investigators.

1.2. Definitions

Primary end point was all cause mortality, which consisted of sudden cardiac death, nonsudden cardiovascular death, and noncardiac death. Sudden cardiac death was defined as witnessed or unwitnessed, instantaneous death in a patient who had no deterioration of CHF for 1 week before death and no chest pain.

1.3. Statistical analysis

Baseline descriptive statistics are presented as the mean ± standard deviation or median (range) for continuous variables and numbers with percentages for categorical variables. Differences between variables in patients with low versus high heart rate were evaluated by Students *t*-test or Mann–Whitney *U*-test, depending on normality of the data, for continuous data and by Fisher exact test or Chi-square test for categorical data.

Kaplan–Meier estimates of cumulative event rates were calculated and all cause mortality for the 2 study groups were compared using log–rank tests. Adjusted hazard ratios were calculated using Cox proportional hazards regression models. A stepwise approach was used. Heart rate dichotomized according to the median value as well as all univariate variables with $p<0.1$ were tested in the multivariate model. Cut-off value of all dichotomized variables was the median value. First-line interactions were investigated. In all analyses a value of $p<0.05$ was considered statistically significant.

2. Results

2.1. Clinical characteristics

In the neurohormonal substudy of PRIME II 372 patients were included. At inclusion atrial fibrillation was present at 2 consecutive 12-lead electrocardiograms in 77 patients. The clinical characteristics are given in Table 1. Most patients were in the NYHA class III for chronic heart failure. Ischemic heart disease was the most common cause of chronic heart failure. Median duration of atrial fibrillation at inclusion was 21 (0–336) months. When dichotomizing the patients according to the median heart rate at baseline (80 bpm), 39 patients had a heart rate ≤80 bpm (the "low" heart rate group, median 72 bpm, range 57–80) and 38 patients had a heart rate >80 bpm (the "high" heart rate group, median 90 bpm, range 81–163, difference $p<0.001$). Patients with a high heart rate had a higher NYHA functional class ($p=0.049$). All other variables did not differ significantly. Ibopamine versus placebo treatment was equally distributed in both groups (56% versus 55%, $p=0.92$), starting after randomization and instituted until discontinuation after early termination of PRIME II. No differences in rate control drugs and antiarrhythmic drugs (mostly amiodarone) were found. Beta-blocker therapy was only rarely instituted at that time.

2.2. Neurohormones

At study entry, the levels of norepinephrine, renin, (N-)ANP, (N-)BNP and endothelin were elevated, irrespective of the heart rate. Plasma levels of epinephrine, dopamine and